REMARKS

With entry of the amendments, claims 1-15 are pending in the application. Claims 12, 14, and 15 stand rejected under 35 U.S.C. 101; claims 5, 6, and 8 stand rejected under 35 U.S.C. 112, second paragraph; claims 12, 14, and 15 stand rejected under 35 U.S.C. 102(b); and claims 1-15 stand rejected under 35 U.S.C. 103(a).

In view of the amendments above and the arguments below, Applicants respectfully request reconsideration on the merits of the application.

New oath or declaration

The Examiner noted that one of the inventors had made a change to the declaration without initialing and dating the change, and he required a new declaration to be submitted. Applicants submit herewith a new declaration. Unfortunately, one of the inventors made a change to her address as provided on the declaration without dating and initialing the change. Therefore, Applicants will resubmit her declaration under separate cover within the next day.

Rejections under 35 U.S.C. 101

Claims 12, 14, and 15 have been amended to clarify that what is claimed are non-human embryos. Because the claims as amended are drawn to statutory subject matter, Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. 112, par. 2

Claim 5 was rejected as being indefinite for the recitation of an enucleated oocyte selected from "the group of bovine oocytes" undergoing nuclear maturation within 16 hours of initiating *in vitro* culture. Applicants have amended claim 5 to clarify that the enucleated bovine recipient oocyte is prepared from a bovine oocyte undergoing nuclear maturation within 16 hours of initiating *in vitro* culture.

Claim 6, which depends from claim 1, was rejected as being indefinite for the recitation of "the enucleated bovine recipient oocyte" because there is no antecedent basis for "bovine". Applicants have amended claim 6 to delete the limitation "bovine" and to clarify that the method is not limited to enucleated bovine recipient oocytes.

Claim 8 stands rejected as being indefinite because it is unclear to what "the incubating" refers. Claim 8 was amended to correct a typographical error by changing "the" to "then".

species is a mammalian species, and differentiated cytoplasm, cell membrane, and nucleus derived from a second species. Support for using a mammalian recipient oocyte is found throughout the specification (e.g., page 7, lines 4-6; page 9, lines 8-12; page 12, lines 23-26; page 23, line 23-page 24, line 33). Applicants respectfully submit that amendments to claims 12, 14, and 15 overcome the rejection of the claims under 102(b) as being anticipated by Gurdon and request that the rejection be withdrawn.

Rejection of claims under 35 U.S.C. 103(a)

Claims 1-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Prather *et al.* (Biology of Reproduction, 1989, Gurdon *et al.* (J. Cell Sci. 1986), Campbell *et al.* (WO 97/07668, March, 1997), Telford *et al.* (Molecular Reproduction and Development, 1990), and Dominko *et al.* (Molecular Reproduction and Development, 1997).

The Examiner characterized Prather *et al.* and Gurdon as teaching methods of trans-species nuclear transfer, wherein the nucleus from a donor of one species is transplanted into an enucleated oocyte of a different species. Applicants respectfully submit that Prather *et al.* does not teach trans-species nuclear transfer, but rather, teaches intraspecies nuclear transfer using pig donor and recipient cells. As discussed in the preceding section, Gurdon teaches nuclear transfer of one species to an enucleated oocyte of a second species, wherein the recipient oocyte was an amphibian oocyte, specifically a frog oocyte. The Examiner stated that, although cross-species nuclear transfer was performed prior to the filing date, "optimization of conditions would be necessary to produce a chimeric embryo capable of longer term culturing or capable of progressing through embryogenesis."

Campbell, Dominko, and Telford are cited as teaching optimization to increase bovine embryo development. Campbell is cited as teaching using donor cells that have been arrested in G_o, maturation curves of bovine oocytes, and activation of the nuclear transfer embryo. Dominko *et al.* was said to teach increased efficiency of embryo development when the genetic material is transferred after greater than 8 hours of culturing. Telford *et al.* was said to teach a transition from maternal control to the embryo, which occurs between 8-16 hours for bovine embryos.

A prima facie case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art,

not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143). Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness for the reasons set forth below.

The art does not teach or suggest all of the claim limitations

The cited art does not combine to teach or suggest all of the claim limitations. Specifically, the cited art does not teach or suggest a nuclear transfer method in which an enucleated mammalian recipient oocyte is fused with a donor cell from a different species to form a nuclear transfer embryo. As discussed in the previous section, Prather teaches intraspecies nuclear transfer in pigs, and Gurdon teaches trans-species nuclear transfer using frog oocytes as the recipient cell.

None of the secondary references cure the deficiencies of the primary references. Campbell teaches using bovine oocytes as the recipient in intraspecies transfers. As the Examiner points out, Campbell teaches using nuclear transfer to generate transgenic animals. However, as one of skill in the art would appreciate, a transgenic animal within the common usage of the term and in accordance with the definition of "transgenic" provided in Campbell (p. 6, lines 24-33) is not an animal derived from an embryo made from an enucleated mammalian recipient oocyte and a donor cell from a different species.

Dominko *et al.* discusses embryo development as a function of time following intraspecific insemination of oocytes. Applicants respectfully submit results from research involving *in vitro* insemination of oocytes does not suggest conditions that would result in successful formation of a trans-species nuclear transfer embryo using a mammalian recipient oocyte.

Telford *et al.* is cited as teaching that the conversion from maternal to embryo control [of transcription] in cows occurs between 8 and 16 hours, and "the skilled artisan would therefore know to deliver the nuclei after the 16 hour culture transition period." The Examiner specifically refers to Table 1, page 93, which shows that the maternal to embryonic control in cow embryos, as measured by a major change in the qualitative pattern of protein synthesis, occurs at cell stage 8-16 (not after 8-16 hours) of embryonic development. As one of skill in the art would appreciate, the conversion from maternal to embryonic control does not occur until after fertilization or, in the case of the present invention, after nuclear transfer. The Telford *et al.* publication does not provide the guidance suggested by the Examiner, nor does Telford *et al.* teach trans-species nuclear transfer using a mammalian recipient oocyte and a donor cell of a different species.

The art provides no suggestion or motivation to make the claimed invention, nor does the art provide a reasonable expectation of success

There is no suggestion in the art of record to modify the references to make the claimed invention. The Examiner, citing In re O'Farrell 7 USPQ2d (BNA) 1673 , asserted that "obviousness does not require absolute predictability of success; all that is required is a reasonable expectation of success." However, as the court points out in In re Vaeck, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be founded in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143). In re O'Farrell is characterized as holding that "the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful." (MPEP 2143.02).

In finding that the PTO erred in rejecting claims as prima facie obvious within the meaning of § 103, the court in In re Vaeck distinguished over an earlier holding in In re O'Farrell, in which the court upheld the PTO's rejection of claims under § 103:

> We thus affirmed, explaining that
>
> > The prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins. Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful. (7 USPQ 2d at 1679-1680).
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> In contrast with the situation in O'Farrell, the prior art in this case offers no suggestion , explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in O'Farrell is not present here. Accordingly, we reverse the § 103 rejections. (In re Vaeck, , 947 F.2d 488, 494-495).

Because there is no suggestion in the art to make a trans-species nuclear transfer embryo using a mammalian oocyte as the recipient, and the art provides no reasonable expectation of success, a prima facie case of obviousness has not been established. Applicants respectfully request that the rejections under 35 U.S.C. 103(a) be withdrawn.

As the application is now in condition for allowance, Applicants request allowance of the claims. Should the Examiner feel that any other point requires consideration or that the

form of the claims can be improved, the Examiner is invited to contact the undersigned at the number listed below.

No fee is believed due in connection with this submission. Please charge any fee due or credit any overpayment of fees to Deposit Account No. 50-0842.

Respectfully submitted,

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donor cell contacts said enucleated oocyte;

fusing said donor cell with said enucleated oocyte by electric pulse at 16-32 hours after the beginning of *in vitro* culture to create a nuclear transfer embryo;

and activating said nuclear transfer embryo by sequential incubation with ionomycin and 6-dimethylaminopurine at 16 to 32 hours after the beginning of *in vitro* culture.

14. [The] A non-human embryo produced by the [process] method of claim 13.

15. A non-human nuclear transfer embryo comprising cytoplasm and cell membrane from [one] a first species, wherein the first species is a mammalian species, and differentiated cytoplasm, differentiated cell membrane, and [nuclei] nucleus derived from a differentiated cell of [another] a second species.